PHARMACOLOGY & THERAPEUTICS

Executive Editors
W. C. Bowman, A. M. Breckenridge, A. C. Sartorelli.

CHEMOTHERAPY

CLINICAL PHARMACOLOGY & THERAPEUTICS

TOXICOLOGY

L.
3
3

METABOLIC INHIBITORS

GENERAL & SYSTEMATIC PHARMACOLOGY

Volume contents, Author index
and Subject index to
Volume 23

PERGAMON PRESS OXFORD · NEW YORK

PHARMACOLOGY & THERAPEUTICS

Chemotherapy, Toxicology and Metabolic Inhibitors

Executive Editor: A. C. Sartorelli

Yale University School of Medicine, Department of Pharmacology, 333 *Cedar Street, New Haven, Connecticut* 06510, *USA*

Associate Editor: John S. Lazo

Managing Editor: Barbara Z. Renkin, Ph.D.

General and Systematic Pharmacology

Executive Editor: W. C. Bowman

University of Strathclyde, Department of Physiology & Pharmacology, Royal College, 204 *George Street, Glasgow G1 1XW, Scotland*

Clinical Pharmacology and Therapeutics

Executive Editor: A. M. Breckenridge

University of Liverpool, Department of Pharmacology & Therapeutics, P.O. Box 147, *Liverpool L69 3BX, England*

Editorial Board

G. E. Adams—*Sutton, Surrey, England*
S. Agoston—*Groningen, Netherlands*
Joseph R. Bertino—*New Haven, Connecticut*
Ernest Bueding—*Baltimore, Maryland*
B. A. Callingham—*Cambridge, England*
Donald S. Coffey—*Baltimore, Maryland*
William A. Creasey—*Philadelphia, Pennsylvania*
P. F. D'Arcy—*Belfast, N. Ireland*
M. A. Denborough—*Canberra, Australia*
Robert L. Dixon—*Research Triangle Park, North Carolina*
Jürgen Drews—*Wien, Austria*
W. F. Dryden—*Edmonton, Alberta, Canada*
B. L. Furman—*Glasgow, Scotland*
George A. Galegov—*Moscow, USSR*
C. F. George—*Southampton, England*
Evgeny Golovinsky—*Sofia, Bulgaria*
Robert E. Handschumacher—*New Haven, Connecticut*
Peter Langen—*Berlin, GDR*
Åke Liljestrand—*Stockholm, Sweden*
Jerry Mitchell—*Houston, Texas*
A. Nies—*Denver, Colorado*
E. E. Ohnhaus—*Essen, German Federal Republic*
M. L'E. Orme—*Liverpool, England*
J. Gy Papp—*Szeged, Hungary*
Robert E. Parks, Jr.—*Providence, Rhode Island*
Sidney Pestka—*Nutley, New Jersey*
William H. Prusoff—*New Haven, Connecticut*
J. L. Reid—*Glasgow, Scotland*
A. Richens—*Cardiff, Wales*
D. S. Savage—*Glasgow, Scotland*
D. G. Shand—*Durham, North Carolina*
David Shugar—*Warsaw, Poland*
F. Sjöqvist—*Huddinge, Sweden*
Jan Škoda—*Prague, Czechoslovakia*
A. Stafford—*Glasgow, Scotland*
Donald J. Tipper—*Worcester, Massachusetts*
E. S. Vesell—*Hershey, Pennsylvania*
George Weber—*Indianapolis, Indiana*
Gerhard Zbinden—*Zürich, Switzerland*

Library Annual Subscription Rates—published in 4 volumes per annum of 3 issues each.
Annual Subscription, 1985, U.S. $800.00 including postage and insurance, 2 years, 1985/86, U.S. $1520.00.
Specially Reduced Rates to Individuals: Any individual whose institution takes out a library subscription may purchase a second or additional subscription for personal use at a much reduced rate of $350.00 annually. Subscribers to the Journal may claim a 20% discount off Encyclopedia volumes.

Subscription enquiries from customers in North America should be sent to Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523, USA, and for the remainder of the world to Pergamon Press Ltd, Headington Hill Hall, Oxford OX3 0BW, England.

At the end of the year, the Subscriber will receive, free, both the annual subject index and an attractive and durable magazine binder, especially designed for *Pharmacology & Therapeutics*.

Copyright © 1984 Pergamon Press Ltd.

It is a condition of publication that manuscripts submitted to this journal have not been published and will not be simultaneously submitted or published elsewhere. By submitting a manuscript, the authors agree that the copyright for their article is transferred to the publisher if and when the article is accepted for publication. However, assignment of copyright is not required from authors who work for organisations which do not permit such assignment. The copyright covers the exclusive rights to reproduce and distribute the article, including reprints, photographic reproduction, microform or any other reproduction of similar nature and translations. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, electrostatic, magnetic tape, mechanical photocopying recording or otherwise, without permission in writing from the copyright holder.

U.S. COPYRIGHT LAW APPLICABLE TO USERS IN THE U.S.A.

The Item-Fee Code for this publication indicates that authorization to photocopy items for internal or personal use is granted by the copyright holder for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service provided the stated fee for copying beyond that permitted by Section 107 or 108 of the United States Copyright Law is paid. The appropriate remittance of $0.50 per page is paid directly to the Copyright Clearance Center Inc., 21 Congress Street, Salem, MA 01970. The copyright owner's consent does not extend to copying for general distribution, for promotion, for creating new works, or for resale. Specific written permission must be obtained from the publisher for such copying. In case of doubt please contact your nearest Pergamon Office.

The Item-Fee Code for this publication is: 0163-7258/84 $0.00 + 0.50

Microform Subscriptions and Back Issues

Back issues of all previously published volumes are available in the regular editions and on microfilm and microfiche. Current subscriptions are available on microfiche simultaneously with the paper edition and on microfilm on completion of the annual index at the end of the subscription year.

Publishing and Advertising Offices

Pergamon Press Ltd.
Headington Hill Hall
Oxford OX3 0BW
England

Pergamon Press Inc.
Maxwell House
Fairview Park, Elmsford
New York 10523, U.S.A.

Volume 23, 1983, Numbers 1–3

CONTENTS

Number 1 PAGE

Clinical applications of slow channel blocking compounds: *A. G. Ellrodt and B. N. Singh* 1

Design and use of potent, specific enzyme inhibitors: *G. R. Stark and P. A. Bartlett* 45

Cholelitholytic agents: *G. D. Bell* 79

Permeabilization of cells during animal virus infection: *L. Carrasco and J. C. Lacal* 109

Targeting potential of antibody conjugates: *D. C. Edwards* 147

Number 2

Class I antiarrhythmic agents: quinidine, procainamide and *N*-acetylprocainamide, disopyramide: *D. M. Roden and R. L. Woosley* 179

The estrogenic and antiestrogenic activities of androgens in female target tissues: *H. Rochefort and M. Garcia* 193

Latency and acquired resistance — problems in chemotherapy of herpes infections: *G. Darby and H. J. Field* 217

Placental drug transfer: effects of gestational age and species: *G. W. Mihaly and D. J. Morgan* 253

Neurohypophyseal hormones and cognition: *B. Strupp, H. Weingartner, F. K. Goodwin and P. W. Gold* 267

Neurohypophyseal hormones in tolerance and physical dependence: *R. F. Ritzmann, D. L. Colbern, E. G. Zimmermann and W. Krivoy* 281

Number 3

Effects of ethanol on thermoregulation: *H. Kalant and A. D. Lê* 313

Pavlovian conditioning of drug-induced changes in body temperature: *C. L. Cunningham, J. C. Crabbe and H. Rigter* 365

Nature and properties of the bacterial ribonucleotide reductases: *H. P. C. Hogenkamp* 393

Enterotoxigenic diarrhea: mechanism and prospects of therapy: *D. W. Powell* 407

Bleomycin — mode of action and particular reference to the cell cycle: *P. R. Twentyman* 417

Progestins can mimic, inhibit and potentiate the actions of androgens: *C. W. Bardin, T. Brown, V. V. Isomaa and O. A. Jänne* 443

AUTHOR INDEX

Bardin, C. W. 443
Bartlett, P. A. 45
Bell, G. D. 79
Brown, T. 443

Carrasco, L. 109
Colbern, D. L. 281
Crabbe, J. C. 365
Cunningham, C. L. 365

Darby, G. 217

Edwards, D. C. 147
Ellrodt, A. G. 1

Field, H. J. 217

Garcia, M. 193
Gold, P. W. 267
Goodwin, F. K. 267

Hogenkamp, H. P. C. 393

Isomaa, V. V. 443

Jänne, O. A. 443

Kalant, H. 313
Krivoy, W. 281

Lacal, J. C. 109
Lê, A. 313

Mihaly, G. W. 253
Morgan, D. J. 253

Powell, D. W. 407

Rigter, H. 365
Ritzmann, R. F. 281
Rochefort, H. 193
Roden, D. M. 179

Singh, B. N. 1
Stark, G. R. 45
Strupp, B. 267

Twentyman, P. R. 417

Weingartner, H. 267
Woosley, R. L. 179

Zimmermann, E. G. 281

SUBJECT INDEX

Abrin, antibody conjugates 163, 165
N-Acetylprocainamide *see also* procainamide
  structure 184
Acyclovir, herpes infected cells 228
Adverse drug reactions
  calcium antagonists, 28, 29
  chenodeoxycholic acid 93, 94
  disopyramide 186
  fetus 260–3
  procainamide 186
  quinidine 182, 183
  ursodeoxycholic acid 98, 99
Androgens
  breast cancer 209, 210
  estradiol competition 198–200
  estrogen antagonism 206–8
  estrogenic activities 201–4
  estrogen receptor effects 197–206
    direct binding 199, 200
  female target tissue effects 193–212
  female tissues stimulated 195, 196
  and β-glucuronidase locus 447, 448
  in vivo effects 196, 197
  kidney protein effects 443–5
  metabolism 194
  nuclear translocation 200, 201
  plasma concentrations 194
  progesterone receptor 203, 204
  progestin effects 443–57
  protein induction in MCF$_7$ cells 204, 205
  receptor antiandrogen binding 454, 455
  receptor kinetics and response 451–4
  receptor and progestin action 450, 451
  role in females 208, 209
  scheme of action in estrogen cells 211
  structures 193, 194
Antiarrhythmic agents
  class I 179–89
  transmembrane potential 179
Antibody
  carrier molecule 147–51
  in vivo localization 150
Antibody conjugates
  A-chain 166–9
  alkylating agents 155–9
  antibiotics 159, 160
  chlorambucil 155–7
  covalent linkage 151–4
  enzymes 161, 162
  methotrexate 155
  non-covalent linkage 151
  –protein 152, 153
  radionuclides 161
  target antigens 148–50
  targeting potential 147–69
  toxins 162–6
  vindesine 160, 161
Arachidonic acid metabolic pathway 411
ATCase (aspartate transcarbamylase) reactions 63

Barbiturates
  hypothalamic activity 305, 306
  neurophyseal peptide release 304–6
  neurophyseal peptides and response 288, 289
Bleomycin 417–36
  cell cycle effects 423–31
    log and plateau phase 424, 425
    normal tissue 430, 431
    phase dependence 423, 424
    progression delay 427
    recovery 427–9
    survival curves 425–7
    therapeutic effects 432
    tumors 429, 430
  DNA damage and cytotoxicity 421, 422
  DNA effects 419–21
  membrane permeability 423
  organelle effects 422
  radiation combination 433, 434
  related compounds 434
  RNA effects 421
  source 417
  structure 418
Bleomycin-inactivating enzyme 422, 423
Body temperature *see also* ethanol, thermoregulation
  drugs used 382, 383
  ethanol conditioning 371–5
  morphine conditioning 371–5

CAD 45
Calcium antagonists
  angina 14–19
  cardiac dysrhythmias 5–9
  clinical uses 1–33
  drug interaction 29–31
  heart failure 24
  hemodynamic effects 12, 13
  hypertension 22, 23
  hypertrophic cardiomyopathy 21, 22
  myocardial effects 9, 10
  myocardial infarction 19, 20
  platelet antagonism 25, 26
  pulmonary disorders 24, 25
  selection 28, 29
  vasculature effects 10–12
  vasospastic angina 14
  vasospastic disorders 24, 25
Calmodulin, antisecretory effects 412, 413
Capmul 8210 and bile acid EDTA
  bile duct infusion 83, 84
Cardiac dysrhythmias, calcium antagonists 5–9
Chenodeoxycholic acid
  drug combinations 91, 92
  gallstone dissolution 88–96
  gallstone recurrence 95, 96
  mode of action 92, 93
  National Co-operative Gallstone Study 89
  side effects 93, 94

Cholelitholytic agents 79–100
bile alteration 99, 100
bile duct, solvents 79–86
bile lipids 86–100
T-tube 84–6
Cognition
altered, mechanisms 268
neurophyseal hormones 267–75
animals 268, 269
man 270, 271
Conditioned and unconditioned stimuli 365–7
discrimination design 369
drug-induced temperature changes 368, 369
ethanol 371–5
evidence for 370, 371
tolerance 384–8
Currents, rapid and slow inward 3, 4
Cyproterone acetate and renal β-glucuronidase 446

Dependence
addictive behavior 389
definition 282
ethanol 339–46
mechanisms of hypothermia 340–6
physical 339, 340
neurophyseal hormones 281–306
Diltiazam
angina 17, 18
cardiovascular therapy 32
clinical pharmacology 26, 28
effects 5
side effects 29
structure 2
Disopyramide 185–8
pharmacokinetics 187, 188
structure 187

Enterotoxigenic diarrhea and intestinal secretion 409
Enzymes, cell culture overproduction 68
Enzyme catalysis 47, 48
inhibitor types 48
Enzyme inhibitors *see also* PALA
affinity labeling 54–6
computer-assisted design 60, 61
design and use 45–71
irreversible 54–60
multisubstrate analogs 49, 50
pyrimidine nucleotide synthesis 61–71
reversible 48–54
suicide 56–60
flavin enzymes 58
hydrolytic enzymes 59, 60
pyridoxal enzymes 57, 58
thymidylate synthetase 58, 59
target enzyme 46
transition state analogs 50–4
uses 45, 46
Ethanol
acetylcholine effects 330
and amino acid transmitters 330, 331
body heat loss 320–3
catecholamine effects 340–2
and chlorpromazine 350
conditioning and body temperature 371–5
dependence 339–46
depressant drug comparison 349, 350
dopamine effects 325–7
β-endorphin effects 332, 333
heat production 318–20
histamine effects 329, 330
5-hydroxytryptamine effects 328, 329, 342, 343
neuronal membrane effects 344–6
neurophyseal peptide release 302–4
neurophyseal peptides and response 283–8
dependence 284, 285
mechanisms 287, 288
tolerance 285–7
norepinephrine effects 327, 328
opiate comparison 349, 350
prostaglandin effects 334, 335
thermoregulation 313–53
thyrotropin releasing hormone 333, 334
tolerance types 336–9
loss 339

Fetal drug exposure
fetal factors 257, 258
maternal factors 256, 257
placental factors 254–6
species differences 258, 259
and susceptibility 259–63
Fetus
adverse drug reactions 260–3
species dependence 262, 263
repair 262

Gallopamine structure 2
Gallstones *see also* cholelitholytic agents
bile lipids 86–8
common bile duct therapies 84–6
formation 86, 87
Gene amplification 68

Heparinized saline, bile duct infusion 81
Herpes virus
cell enzyme activities 221
–cell interactions 222–4
diseases caused 218
latency 224, 225
man 217, 218
neurotropic 217–19, 222–8
recrudescence 227
replication 219–22
resistance 230–9
sites infected 225
TK defective 232–4
Herpes virus chemotherapy 228–30
animal studies 236, 237
drugs used 226, 227
latency effects 239–42
man 237–9
reactivation 241, 242
resistance 230–9
Hygromycin B, cell membrane effects 135

Intestinal water and electrolyte transport 407–11
antisecretory agents 411–14
calcium stimulated 410
kinin stimulated 410
mediators 408–11
transport 407–11

Latency in herpes virus 224, 225
drug effects 239, 240
features 239
D-Limonene, bile duct infusion 84
Lysolethicin 136

Membrane permeabilization
animal virus infection 109–38
viruses 118
ATP effects 136, 137
cell metabolism effects 126–30
DNA viruses 124–6
drugs affecting 132–7
late virus infection 117
leakiness 113, 114
molecule movements 115–17
potential modifications 114, 115
RNA synthesis 128, 129
RNA viruses 119–24
viral functions 130–2
Memory and vasopressin 271–4
Metronidazole and gallstones 99
Monensin
membrane permeabilization 132–7
structure 133
Mono-octanoin, bile duct infusion 81–3
Morphine
body temperature conditioning 375–82
dependence 380, 381
humans 381, 382
hyperthermia 371–9
hypothermia 375, 376, 378, 379
neurophyseal hormones and response 291–5
dependence 291–3
tolerance 293–5

Neuropeptides, ethanol effects 332–4, 343, 344
Neurophyseal hormones 281–306
cognition 267–75
drug effects 281
ethanol response 283–8
psychiatric illness 274, 275
Nifedipine
angina 16, 17
cardiovascular therapy 32
clinical pharmacology 26
effects 5
structure 2
Nigericin
HeLa cell membrane effects 134
membrane permeabilization 132–7
structure 133
Non-steroidal anti-inflammatory drugs, antisecretory gut effects 413
Nucleoside deaminases, inhibitors 52, 53

Opiates, antisecretory effects 413, 414
Opioids
hypothalamic effects 300
neurophyseal peptide release 298–301
neurophyseal peptides and response 289–95
Oxytocin, drug effects 295–306

PALA (*N*-(phosphonacetyl)-L-aspartate) 45
ATCase 63
metabolic interactions 69, 70
orotidylate decarboxylase inhibition 65–7
probe use 64, 65
synthesis 63, 64
therapeutic index 70, 71
Peptidases, enzyme inhibitors 51, 52
Placental drug transfer 253–64 *see also* fetus
fetal exposure 254–6
Platelets, calcium antagonists 25, 26
Procainamide 184–6
electrophysiological effects 184
pharmacokinetics 184–6
Progestins
androgen receptor 450, 451
androgen-responsive organs 448–50
antiandrogenic actions 445–7
binding proteins 455, 456
β-glucuronidase locus 447, 448
kidney protein effects 443–5
synandrogenic actions 445–7

Quinidine 179–83
clinical use 183
electrophysiological effects 180
features 179
pharmacokinetics 180–3
structure 181

Ribonucleotide reductases, bacterial 393–403
adenosylcobalamin-dependent 398–402
antibiotic structures 396
Corynebacterium nephridii 401, 402
features 393, 394
Lactobacillus leichmannii 398–401
manganese-dependent 402, 403
non-heme 394–8
Thermus X–1 402
T_4 phage induced 397, 398
Ribosome inhibiting proteins, antibody conjugates 166–9
Ribulose biphosphate carboxylase inhibitors 53, 54
Ricin, antibody conjugates 163, 165, 166

Slow channel blockers *see* calcium antagonists
Sodium cholate, bile duct infusion 79–81
Supraventricular arrhythmias, calcium antagonists 6–8

Talisomycin 434, 435
Targeting, antibody conjugates 147–69
Testosterone, kidney β-glucuronidase 445
Thermoregulation *see also* body temperature, ethanol
behavioral 335
central mechanisms 323–35
dynamic thermal equilibrium 317, 318
ethanol effects 313–53
animal experiments 315–17
biological significance 351, 352
case reports 313
human experiments 314, 315
hypoglycemia 320
neural connections 331
Tipamil structure 2
Tolerance
conditioning studies 384–8
cross 386, 387
ethanol 335–46
expression manipulation 387, 388

forms 283
neurophyseal hormones 281–306
Toxins *see also* enterotoxins
antibody conjugated 162, 163
diphtheria 162–5

UMP pathway and incorporation 62
Ursodeoxycholic acid
gallstone dissolution 96–9
mode of action 97
side effects 98, 99

Vasopressin
central and peripheral levels 296–8
drugs affecting 295–306
ethanol effects 302, 303
hypothalamic effects 303
and memory 271–4
opioids and release 298–301
Ventricular arrhythmias, calcium antagonists 9
Verapamil
angina 14–17
cardiovascular therapy 32
clinical pharmacology 26–8
effects 5
side effects 28, 29
structure 2
Virus infection *see also* herpes
cell permeabilization 109–38
entry methods 110–13
herpes 126
papova virus 125
picornavirus 120, 121
poxvirus 126
togavirus 121, 122

Zanchol 99, 100

PHARMACOLOGY & THERAPEUTICS

Aims and Scope

Pharmacology and Therapeutics presents lucid, critical and authoritative reviews of currently important topics in pharmacology. The articles are normally specially commissioned, although uninvited review papers are occasionally published. When all the manuscripts covering a certain topic have been published, they are reappraised and, if necessary, updated, and then published as a definitive hard bound volume of the *International Encyclopedia of Pharmacology and Therapeutics.*

This policy ensures that each article is published immediately and is not delayed by the later arrival of other manuscripts for the Encyclopedia volume.

Invitation to Authors

Uninvited reviews will be welcomed for editorial consideration and authors should write to the relevant Executive Editor to obtain guidance on how to prepare their manuscripts prior to submitting their reviews.

International Encyclopedia of Pharmacology and Therapeutics—Editorial Board

W. C. Bowman—*Strathclyde*
D. C. Bovet—*Rome*
A. M. Breckenridge—*Liverpool*
A. S. V. Burgen—*London*
J. Cheymol—*Paris*
G. B. Koelle—*Philadelphia*
P. Lechat—*Paris*
H. Rašková—*Prague*
A. C. Sartorelli—*New Haven*
V. V. Zakusov—*Moscow*

Some Recent and Forthcoming Encyclopedia Volumes

Section 110 The Chemotherapy of Psoriasis
Editor: *H. P. Baden*
ISBN 0 08 029823 0

Section 111 Viral Chemotherapy, Vol. 1
Editor: *D. Shugar*
ISBN 0 08 029821 4

Section 112 Pain and Its Management
Editors: *N. E. Williams and H. Wilson*
ISBN 0 08 029822 2

Section 113 Differentiation Toxicities of Insecticides and Halogenated Aromatics
Editor: *F. Matsumura*
ISBN 0 08 029826 5

Section 114 Nicotine and the Tobacco Smoking Habit
Editor: *D. J. K. Balfour*
ISBN 0 08 030779 5

Section 115 Modulation of Immunology
Editor: *M. S. Mitchell*
ISBN 0 08 031977 7

Section 116 Viral Chemotherapy, Vol. 2
Editor: *D. Shugar*
ISBN 0 08 031985 8

Subscribers to the Journal Pharmacology and Therapeutics may purchase individual volumes of the encyclopedia at a 20% reduction on the published price.

Send to your nearest Pergamon Office for details.